Exhibit A

[redacted]

THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) [redacted]
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

SUPPLEMENTAL REBUTTAL EXPERT REPORT OF STEVEN F. DOWDY, Ph.D.

knowledge in the art, a POSA would have understood that the exon skipping activity of H53A(+23+47) 2'OMePS ASO would be maintained in its corresponding PMO format. *See supra* § IV.A.2.b.iii. Many researchers have confirmed this understanding, including, for example, Dr. Hastings in her work with CERI, Sarepta, and NS. *See* Hastings Supp. Rep. ¶172 (CERI testing confirming that H53A(+23+47) PMO induced exon 53 skipping); Sazani PCT '586, 75-76 (Sarepta scientists confirming that H53A(+23+47) peptide conjugated PMO induced exon 53 skipping); '217 Patent, Figure 18 (NS scientists confirming skipping induced by H53A(+23+47) PMO, labeled "PMO No. 16").

106. Dr. Hastings also argues that H53A(+23+47) cannot be representative of the full scope of the claimed genus because it was tested without base or end modifications. Hastings Supp. Rep. ¶106. But I understand that the written description requirement does not demand examples or an actual reduction to practice (e.g., making ASOs that fall within the claimed genus). Dowdy Reb. Rep. ¶12. Further, H53A(+23+47) is structurally and functionally representative of ASOs with modified bases because both include the same core structures responsible for Watson-Crick base pairing. *See supra* § IV.A.1.b.ii. It is also representative of ASOs with different end modifications, as end modifications are not core structural features of the claimed ASOs and do not participate in Watson-Crick base pairing (and are not even recited in the claims). *See supra* § IV.A.1.b.iii.

107. Dr. Hastings also contends that the reported skipping activity of H53A(+23+47) ("very faint skipping to 50 nM") does not meet the definition of "efficient antisense molecule" provided in the Wilton Patents. Hastings Supp. Rep. ¶86; *see also id.*, ¶111. But the claims of the Wilton Patents simply recite that the claimed ASOs "induce[] exon 53 skipping." Moreover, a POSA reading the Wilton Patents would have understood that any exon skipping was a meaningful

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achievement, worth further pursuit and optimization. Moreover, as Dr. Wilton explained, the inventors of the Wilton Patents [redacted]—using normal skeletal muscle cells to test exon 53 skipping. '851 Patent, cols. 32-33; Wilton Tr. 25:1-8. In these cells, exon skipping ASOs create aberrant, out-of-frame transcripts that are subject to degradation. In contrast, [redacted]. *See* Wilton Tr. 135:3-136:2. A POSA would have understood that observing skipped transcripts in the assay reported in the Wilton Patents is therefore particularly meaningful, regardless of whether skipping is strong or faint.[10]

108. In a footnote, Dr. Hastings criticizes the manner in which the Wilton Patents summarize the exon 53 skipping data, contending that "a POSA would not put much stock in the specification's . . . qualitative report of SEQ ID NO: 195 having supposedly achieved any skipping." Hastings Supp. Rep. ¶110 n.16. But, other than her subject disbelief, Dr. Hastings identifies no specific evidence indicating that a POSA would have doubted the disclosure of the specification. *See id.* In contrast, [redacted] Dowdy Reb. Rep. ¶153; Adams Tr. 49:1-50:2; Wilton Tr. 154:18-23.

[10] Pointing to H53A(+39+69), Dr. Hastings also argues that "a 100% complementary ASO outside the claimed genus ostensibly exhibit[ing] 'Strong skipping' does not mean that a POSA would understand the inventors to possess therapeutic ASOs within the genus." Hastings Supp. Rep. ¶110. But the claims of the Wilton Patents are ***not directed to "therapeutic ASOs."*** *See id.* Nor do they require "therapeutic levels of activity." *Id.* Moreover, Dr. Hastings disregards the importance of H53A(+39+69). Although it does not embody all of the claimed structural features, it helps to define the exon 53 hot spot and therefore contributes to demonstrating the inventors' possession of the claimed PMOs.

[redacted]

109. Dr. Hastings' "visuals," which allegedly "illustrate SEQ ID No: 195's dissimilarity . . . from later-discovered species," are irrelevant. *See* Hastings Supp. Rep. ¶112. As reproduced below, her visuals include an axis titled "Strength of Skipping." The claims of the Wilton Patents, however, simply require "induc[ing] exon 53 skipping." There is no dispute that all three depicted species, H53A(+23+47), Sarepta's Vyondys 53 (golodirsen), and NS's Viltepso (viltolarsen), induce exon 53 skipping. *See* Dowdy Reb. Rep. ¶111. As such, H53A(+23+47) is functionally representative of the other two species, which also induce exon 53 skipping.

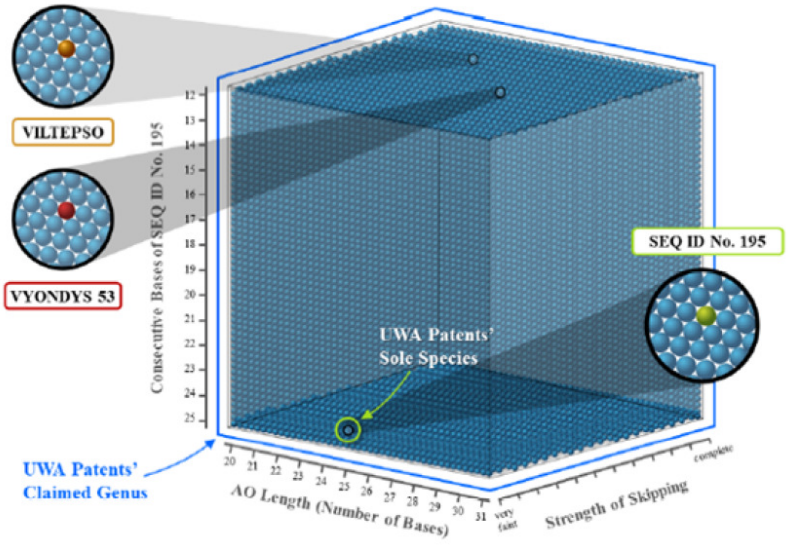

Figure 6. "Visuals" Excerpted from Dr. Hasting's Supplemental Report (Hastings Supp. Rep. ¶112)

110. Another axis in her visual is labeled "Consecutive Bases of SEQ ID NO: 195," which appears to represent the number of consecutive bases of SEQ ID NO: 195 that the claimed PMOs contain. But the claims of the Wilton Patents simply require comprising "at least 12 consecutive bases" of SEQ ID NO: 195. There is no dispute that all three depicted species, H53A(+23+47), Sarepta's Vyondys 53 (golodirsen), and NS's Viltepso (viltolarsen), contain "at least 12 consecutive bases" of SEQ ID NO: 195. *See* Dowdy Reb. Rep. ¶111. As such, H53A(+23+47) is structurally representative of the other two species.

[redacted]

111. NS's "visuals" also ignore other structural features shared by the three depicted species, including, for example, 100% complementarity to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, as well the target region being within nucleotides +23 to +69 of exon 53. When all of the claimed structural and functional features are appropriately accounted for, H53A(+23+47) is both structurally and functionally representative of Dr. Hastings' "later-discovered species." *See* Dowdy Reb. Rep. ¶111 (Table 17).

	H53A(+23+47)	**Viltolarsen**	**Golodirsen**
"antisense oligonucleotides"	✓	✓	✓
"20 to 31 bases"	✓	✓	✓
"a base sequence that is 100% complementary to consecutive bases"	✓	✓	✓
"a target region of exon 53 of the human dystrophin pre-mRNA"	✓	✓	✓
"at least 12 consecutive bases of [SEQ ID NO: 195]"	✓	✓	✓
"morpholino" w/ "thymine"	**X** (Table 1A states that this ASO can be made as "morpholino" with "T")	✓	✓
"the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69)"	✓	✓	✓
"induces exon 53 skipping"	✓	✓	✓

112. None of Dr. Hastings' other arguments changes my opinion. Dr. Hastings contends that a single disclosed species cannot be representative of the claimed genus of ASOs in view of alleged unpredictability. Hastings Supp. Rep. ¶¶95-105, 107, 108, 110. I understand that there is no set requirement as to the number of species that must be disclosed to adequately describe a claimed genus. Dowdy Reb. Rep. ¶12. Regardless, as explained above, Dr. Hastings' unpredictability allegation fails for multiple reasons, as the teachings of the Wilton Patents

[redacted]

overcame background unpredictability for exon 53 skipping ASOs having the structural features recited in the claims. *See supra* § IV.A.2.b.ii.

113. In sum, a POSA would have concluded that the specification of the Wilton Patents discloses a representative species, H53A(+23+47).

4. Response to Dr. Hastings' Other Arguments

a. Dr. Hastings' Additional Lab Notebook Review

114. In her Opening Report, Dr. Hastings argued that select experiments from Dr. Wilton's laboratory support her opinion that the claims lack adequate written description. *See* Hastings Op. Rep. ¶¶74-87. I previously addressed Dr. Hastings' erroneous interpretation of these experiments in my Rebuttal Report. *See* Dowdy Reb. Rep. ¶¶149-187.

115. In her Supplemental Report, it appears that Dr. Hastings has altered her prior analysis in two ways, with underlined text showing additions to her prior argument: (1) [redacted] Hastings Supp. Rep. ¶138.

116. It is unclear what Dr. Hastings means by an "equivalent" sequence. [redacted] *See* Adams Tr. 30:10-25; Wilton Tr. 155:5-25. [redacted] Dowdy Reb. Rep. ¶157. [redacted] *See id.*; Errington 2003, 525 (the skipping effects of ASOs are "mediated by a true antisense mechanism").

[redacted]

117. In her Supplemental Report, Dr. Hastings also contends that "Dr. Wilton has studied several other exons, but I was unable to locate even a single instance in any patent, publication, [redacted] in which he referred to as a region of another exon as a 'hot spot.'" Hastings Supp. Rep. ¶148. Dr. Hastings then contrasts the exon 53 data from the Wilton Patent with exon 3 data from the Wilton Patents (*id.*, ¶¶149-150) as well as exon 43 data reported in Wilton PCT '350 (*id.*, ¶¶151-152). Based on data from these other exons, Dr. Hastings contends that "it is not possible to identify a hot spot from the limited data presented in Exon 53 in the '851 Patent." *Id.*, ¶153.

118. I disagree with these additional arguments. *First*, as I previously explained, the term "hot spot" is a colloquial term used in molecular biology for an area where ASOs show high activity. Dowdy Tr. 72:1-22. Whether or not Dr. Wilton used that term is irrelevant to what a POSA would have understood from the data disclosed in the Wilton Patents. *See*, *e.g.*, Fletcher Tr. 118:2-9 [redacted].

119. *Second*, Dr. Hastings fails to explain how, if at all, the presence or absence of a hot spot for ***exon 3*** or ***exon 43*** is relevant to the claimed inventions of the Wilton Patents, which are directed to ***exon 53*** targeting ASOs. Whether or not overlapping ASOs induced exon 3 or exon 43 skipping is irrelevant to the disclosure of the exon 53 hot spot based on data obtained from H53A(+23+47), H53A(+39+62), H53A(+45+69), and H53A(+39+69), each of which induces exon 53 skipping. *See* '851 Patent, Table 39. In any event, the exon 3 data cited by Dr. Hastings indicates a narrow region of activity around positions 30 to 50, such that ASOs directed to that region would have a higher chance of inducing exon 3 skipping (e.g., H3A(+30+50)) than those that only partially overlap with that region (e.g., H3A(+37+61)). The data relating to exon 43 was

[redacted]

not available in June 2005, and thus could not reflect the understanding of a POSA as of that time. Wilton PCT '350, item (22). Notably, Dr. Hastings has been ***unable to identify or even deliberately design*** any ASO meeting the structural characteristics of the claims that does not induce skipping of exon 53. *See generally* Hastings Supp. Rep.

120. *Third*, numerous studies from multiple independent research groups repeatedly confirmed Dr. Wilton's exon 53 hot spot. *See* Dowdy Reb. Rep. § V.A.2.c. [redacted], it indisputably induces exon 53 skipping. *See supra* § IV.A.3.

121. In sum, Dr. Hastings' attack against Dr. Wilton's ***exon 53*** hot spot based on ***exon 3*** or ***exon 43*** targeting ASOs is a red herring.

b. Dr. Hastings' Reinterpretation of the [redacted]

122. Dr. Hastings again relies on three studies [redacted]. Hastings Supp. Rep. ¶157. In my Rebuttal Report, I addressed each study and explained that the [redacted] Dowdy Reb. Rep. ¶¶188-220. Specifically, I explained that [redacted] *Id.*, ¶211.

123. The Court's clarified claim construction further strengthens my opinion, [redacted] while the majority of ASOs outside the scope of the claim do not induce exon 53 skipping. *See supra* § III.B. As shown below, [redacted]

CERTIFICATE OF SERVICE

I hereby certify that on August 14, 2024, copies of the foregoing were caused to be served upon the following in the manner indicated:

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